Please amend the subject application as follows:

In the Claims

Please cancel Claims 2-3, 11-12 and 19-20.

REMARKS

The Examiner's withdrawal of several of the rejections made in Paper No. 6 under 35 U.S.C. §§ 112, first and second paragraphs, including the deposit requirement, and the rejection under 35 U.S.C. § 103 is acknowledged with appreciation.

Applicant's Claim for Priority

It is Applicants' position that the amended claims are entitled to a priority date of October 8, 1992, the filing date of U.S.S.N. 07/958,248 (the '248 application).

It is noted that the Examiner has not provided a reason why each claim lacks support for priority. It is believed that the initial burden is upon the Examiner to provide an explanation in support of such a conclusion. See M.P.E.P. § 201.15, for example.

The '248 application, at page 4, lines 27-32, describes the treatment of autoimmune disease and inflammatory disease (such as rheumatoid arthritis) with anti-CD4 antibodies and anti-TNF antibodies (see also, e.g., page 6, lines 5-8). At page 11, line 17 to page 12, line 4, the '248 application describes autoimmune and acute and chronic inflammatory diseases, specifically listing Crohn's disease and rheumatoid arthritis.

At page 10, lines 6-9, the '248 application specifically recites the use of methotrexate in conjunction with an anti-TNF antibody. At page 6, lines 8 to page 7, line 26, the '248 application describes anti-TNF antibodies (see also page 8, lines 13-33). At page 11, lines 1-6, the '248 application describes the use of other agents which interfere with TNF, TNF receptor signalling or TNF synthesis (TNF antagonists).

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Thus, the '248 specification provides support for these claims. Similarly, the remaining parent applications provide support for these claims. Accordingly, the claims are entitled to a priority date of October 8, 1992, the filing date of the '248 application.

With regard to the claims which recite characteristics of the preferred anti-TNF antibody, cA2, these claims are patentable even if the Examiner's determination of the effective filing date (as set forth in Paper No. 6) is correct.

Objection to the Specification and Rejection of Claims 1-3, 5-9 and 31 Under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 1-3, 5-9 and 31 rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to use the invention to treat any autoimmune or inflammatory disease encompassed by the claimed methods for the reasons of record set forth in Paper No. 6. It is unclear from this record which of the reasons set forth in Paper No. 6 the Examiner is continuing to rely upon in view of the amendments to the claims. Much of the repeated reasons are not relevant to the claims. Generally, the Examiner states that it would require undue experimentation to practice the claimed invention with a reasonable expectation of success because of (1) the lack of predictability of the art; (2) the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions; (3) the absence of a specific and detailed description in the specification of how to effectively practice the claimed invention; and (4) the absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting autoimmune or inflammatory diseases. Applicants disagree with this assessment.

Claims 2 and 3 have been cancelled.

To be enabling under 35 U.S.C. § 112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02.

The specification teaches that autoimmune and inflammatory diseases can be treated in an individual by co-administering methotrexate and a TNFα antagonist to the individual in therapeutically effective amounts. Examples of autoimmune and inflammatory diseases that can be treated are disclosed in the specification, for example, at page 8, line 28 to page 9, line 3; and page 9, lines 12-27. The Examiner has provided no evidence or technical reasoning to support the conclusion that results described herein cannot be extrapolated to these related diseases. It is noted that neither sepsis nor cachexia (the only disease states which were questioned in Paper No. 6) is listed as an autoimmune or inflammatory disease.

Examples of TNFα antagonists that can be used in the claimed invention are provided in the specification, for example, at page 12, line 29 to page 35, line 11). Guidelines for route of administration and dosages are provided in the specification, for example, at page 35, line 28 to page 39, line 26.

Applicants have exemplified the claimed methods using monoclonal anti-TNFα antibody cA2 in patients with active rheumatoid arthritis (see specification, e.g., Examples 1-3). Since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNFα), it is expected, based upon scientific reasoning, that the claimed methods work in the same manner using other anti-TNFα antibodies as well as other TNFα antagonists. It is also expected, based upon scientific reasoning, that the claimed methods work in the same manner for other autoimmune and

inflammatory diseases, known to be mediated by TNFα. The Examiner has provided no technical or scientific reasoning to the contrary.

Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to use the claimed invention without undue experimentation.

The Examiner states that:

> although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions . . . In human diseases, patients are treated generally after the onset of disease and not prior to disease.

As discussed in Amendment A, these possible difficulties which may be encountered in therapy have been rebutted by clinical data in patients after onset of disease. Also, it is noted that the Examiner has not supplied any basis for this conclusion, e.g., a reference. As the present specification provides human clinical data of the claimed co-administration, the argument is not fully understood and is erroneous. In this instance, the use of antibodies in treating autoimmune diseases, such as RA and Crohn's disease, has been further supported by human clinical data. The extrapolation of animal data to the human condition has been validated with anti-TNFα antibody, particularly when the antibody is used in the mouse after onset of disease as one does in human patients. One skilled in the art would reasonably expect that the invention would work with other members of the genus. Further, with regard to the issue of when

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patients are treated, prevention has been canceled to avoid the issue. If the Examiner intends to maintain this argument, the documentation relied upon for this argument is requested.

The Examiner goes on to state in the rejection that:

> it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation. Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

Claims 1, 5-9 and 31 relate to methods of treating diseases in an individual which belong to an art-recognized class and are known in the art, or are otherwise accepted by those skilled in the art, to be mediated by TNFα. The methods comprise co-administering methotrexate and an anti-TNFα antibody or other TNFα antagonist to the individual. The fact that the cytokine requirements for particular types of inflammation may be different is irrelevant to the issue. The claims do not embrace the treatment of diseases where TNFα does not play an important role in the disease. The claims also do not embrace targeting "any TNF". One skilled in the art would reasonably expect that the results exemplified in the specification for patients with RA are representative of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. That is, one skilled in the art would reasonably find the results exemplified in the specification for RA patients to be reasonably predictive of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. Thus, one skilled in the art would accept the assertions in the

specification as true and enabling. No evidence to the contrary has been presented, only unsupported conclusions.

In response to Applicants' argument, the Examiner contends that the cytokine requirement

> is a critical point as it has been art known that antagonizing a particular cytokine such as TNF may be beneficial in certain diseases, targeting the same cytokine in different inflammatory conditions would not lead to any alleviation of symptoms or disease.

Applicants disagree with this conclusion. The Examiner has not provided the documentation relied upon for this conclusion. One skilled in the art would reasonably expect that targeting TNFα in the diseases recited in the claims would reasonably lead to alleviation of symptoms or disease. If the Examiner intends to maintain this argument, the documentation relied upon in support of the argument is requested.

The Examiner also contends that:

> it has been known that a number of inflammatory mediators including TNFα may be associated with a number of inflammatory diseases, but treating a disease via a particular mediator is not necessarily predictive from one disease to another.

Again, the documentation relied upon for this assertion has not been provided and is respectfully requested if the Examiner intends to maintain the argument. As discussed above, one skilled in the art would reasonably expect that the results exemplified in the specification for patients with RA are representative of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. That is, one skilled in the art would reasonably find the results exemplified in the specification for RA patients to be reasonably predictive of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. Thus, given the guidance provided in the specification, it would not require undue experimentation for one skilled in the art to

practice the claimed invention with a reasonable expectation of success.

The Examiner states that Natanson *et al.* (*Ann. Int. Med.*, *120*(9):771-783 (1994)) teach that murine anti-TNF antibodies have not been beneficial in treating sepsis and septic shock and that targeting TNF may be harmful. The Examiner further states that Claims 1-3, 5-9 and 31 "read on treating any number of inflammatory diseases, including sepsis and cachexia." Applicants respectfully disagree with this conclusion.

Neither sepsis nor cachexia is listed in the present specification as an autoimmune or inflammatory disease (see, e.g., page 8, line 28 to page 9, line 3; and page 9, lines 12-27). Thus, Claims 1, 5-9 and 31 do not read on treating sepsis or cachexia.

In view of the foregoing discussion, withdrawal of the objection to the specification and rejection of Claims 1, 5-9 and 31, under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of Claims 1-3 and 5-31 Under 35 U.S.C. § 103

Claims 1-3 and 5-31 have been rejected under 35 U.S.C. § 103 as being unpatentable over Le *et al.* (U.S. Patent No. 5,656,272) and Aggarwal *et al.* (U.S. Patent No. 5,672,347) in view of Barrera *et al.* (*Cytokine*, *3*(5):504 (1991), Abstract 330), Kozarek *et al.* (*Ann. Int. Med.*, *110*:353-356 (1989)), Markowitz *et al.* (*J. Ped. Gastroent. Nutr.*, *12*:411-423 (1991)), Brahn *et al.* (*Arth. Rheum.*, 32(Suppl. 4):S133 (1992), Abstract D42), Cohen *et al.* (*Rev. Esp. Rheumatol.*, *20*(Suppl. 1):148 (1993), Abstract 318), and Pascalis *et al.* (*Rev. Esp. Rheumatol.*, *20*(Suppl. 1):148 (1993), Abstract 319).

Applicants' invention relates to methods of treating an autoimmune or inflammatory disease (Claims 1-3, 5-9 and 31), rheumatoid arthritis (Claims 10-17) or Crohn's disease (Claims 18-25) in an individual comprising co-administering methotrexate and an anti-TNFα antibody (or, in the case of

Claim 31, a TNFα antagonist) to the individual. Applicants' invention also relates to a composition comprising methotrexate and an anti-TNFα antibody (Claims 26-30).

Teachings of the Cited References

The Primary References

Le *et al.*

The Le *et al.* patent discloses the use of TNF antagonists in the treatment of TNF-related pathologies, including rheumatoid arthritis, Crohn's pathology and ulcerative colitis. The cited patent further discloses that the TNF antagonists can be administered either as individual therapeutic agents or in combination with other therapeutic agents (Le *et al.*, col. 35, l. 25-28).

Several clinical studies are described in the cited patent in which patients with rheumatoid arthritis (RA), Crohn's disease or ulcerative colitis were treated with an anti-TNFα antibody (see Le *et al.*, col. 58 to col. 79 (Examples XX to XXIII)). All disease-modifying anti-rheumatic drugs (DMARDS), such as methotrexate, were discontinued at least one month prior to treatment with anti-TNFα antibody (see, e.g., col. 71, l. 43-44; see also Tables 5, 6 and 12). Thus, the Le *et al.* patent does not exemplify co-administering methotrexate and an anti-TNFα antibody (or other TNFα antagonist) to an individual to treat the disease.

The Examiner states that:

> Even though the particular patient populations employed in the referenced clinical trials were refractory to standard DMARD including methotrexate treatment, it would have been obvious to the ordinary artisan that the combination of standard methotrexate in combination with a highly effective TNF antagonist such as cA2 would be similarly effective for treating patients with inflammatory conditions already being treated with standard methotrexate as well as a TNF antagonist.

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Indeed, it would not be obvious to administer an ineffective drug with an effective drug. There would be no reason to do so. This is a very different situation than presented in *In re Kerkhoven,* 205 U.S.P.Q. 1069 (C.C.P.A. 1980), relied upon by the Examiner. Further, this does not lead to the conclusion that the unexpected results achieved by Applicants by combination therapy with methotrexate and a TNFα antagonist (see, e.g., Example 1 of the specification) were predictable. In particular, based on the teachings of the cited patent, those of ordinary skill in the art would not reasonably conclude that synergistic effects would be obtained by combination therapy with methotrexate and a TNFα antagonist. In fact, there is nothing of record which would indicate that those of ordinary skill in the art would reasonably conclude that synergistic effects would be expected by combination therapy with methotrexate and a TNFα antagonist.

In addition, based on the teachings of the Le *et al.* patent, those of ordinary skill in the art would not reasonably conclude that high clinical response rates for significantly longer durations in comparison with that obtained with treatment with each therapeutic modality separately would be obtained by combination therapy. Those of ordinary skill in the art also would not reasonably conclude, based on the teachings of the cited patent, that significantly reduced immunogenicity of anti-TNFα antibodies would be obtained by combination therapy with methotrexate. Thus, the present invention is characterized by surprising and nonobvious results.

At page 5 of the Office Action (Paper No. 10), the Examiner appears to dispute Applicants' assertions in Amendment A (Paper No. 8) with respect to Examples 1 and 2 of the specification. However, it is not seen that the Examiner's summary of the results disclosed in each of these examples is inconsistent with Applicants' assertions relating to the respective example. Specifically, the Examiner's summary of the results disclosed in Example 1 is consistent with Applicants' assertions relating to the same example: that combination therapy with methotrexate and

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anti-TNFα produced markedly superior results than the results obtained with each reagent alone, particularly at low doses of methotrexate and that significant improvement of the combination therapy was observed even in comparison to where optimal dosages of anti-TNFα antibody were administered alone (see Amendment A at page 25). The Examiner's summary of the results disclosed in Example 2 is also consistent with Applicants' assertion relating to the same example: that combination therapy with methotrexate and anti-TNFα antibody produced a rapid and sustained reduction in the signs and symptoms of the treated autoimmune disease (see Amendment A at page 25).

Aggarwal *et al.*

The Aggarwal *et al.* patent indicates that TNF antagonists can be used in conjunction with other anti-inflammatory agents (e.g., cyclosporin) in the treatment of inflammatory or immune-potentiated inflammatory events (e.g., graft versus host reaction, arthritis, Crohn's disease) (Aggarwal *et al.*, col. 7, l. 60-63) and that "when employed together with TNF antagonists these agents may be employed in lesser dosages than when used alone" (Aggarwal *et al.*, col. 7, l. 65-67). In Example 4, the cited patent sets forth results of preliminary experiments that indicate that the administration of anti-rMuTNFα to mice decreases the severity of graft versus host reaction in the mice as determined by the Simonsen spleen weight assay.

The cited patent does not teach or suggest that synergistic effects would be achieved by combination therapy with methotrexate and a TNFα antagonist. The cited patent also does not teach or suggest a composition comprising methotrexate and a TNFα antagonist.

The Examiner states that the Aggarwal *et al.* patent teaches:

> the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that, in some instances, this combination permits

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one agent to be used in lesser amounts, thereby counteracting any toxic effects.

This, however, does not lead to a conclusion that those of ordinary skill in the art would have predicted the unexpected results achieved by Applicants by combination therapy with methotrexate and a TNFα antagonist (see Examples 1-3 of the specification). Specifically, based on the teachings of the Aggarwal *et al.* patent, those of ordinary skill in the art would not reasonably conclude that synergistic effects would be obtained by combination therapy with methotrexate and a TNFα antagonist. In fact, there is nothing of record which would indicate that those of ordinary skill in the art would reasonably conclude that synergistic effects would be expected by combination therapy with methorexate and a TNFα antagonist.

In addition, based on the teachings of the cited patent, those of ordinary skill in the art would not reasonably conclude that high clinical response rates for significantly longer durations in comparison with that obtained with treatment with each therapeutic modality separately would be obtained by combination therapy with methotrexate and a TNFα antagonist. Those of ordinary skill in the art also would not reasonably conclude, based on the teachings of the Aggarwal *et al.* patent, that significantly reduced immunogenicity of anti-TNFα antibodies would be obtained by combination therapy with methotrexate. Thus, the present invention is characterized by surprising and nonobvious results.

The Secondary References

None of the secondary references cited by the Examiner teach or suggest treating RA, Crohn's disease or other autoimmune or inflammatory disease in an individual by co-administering methotrexate and a TNFα antagonist to the individual. In addition, none of the secondary references teach or suggest a composition comprising methotrexate and a TNFα antagonist. The

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teachings of each of the cited secondary references follow under separate headings.

Barrera *et al.*

Barrera *et al.* disclose in their abstract the use of low-dose methotrexate for treating patients with rheumatoid arthritis. They report that "three patients with highest values of stimulated IL-1β and TNF showed a decrease of more than 50% after MTX" (Barrera *et al.*, second sentence from end). Barrera *et al.* conclude that low-dose methotrexate treatment "seems to induce changes in IL-1β and TNF production in some RA patients" (Barrera *et al.*, last sentence).

Kozarek *et al.*

Kozarek *et al.* report the results of an open-label study of methotrexate treatment in patients with refractory inflammatory bowel disease, including Crohn's disease. They found that methotrexate induced clinical and histologic remission in some patients.

Markowitz *et al.*

The Markowitz *et al.* reference is cited by the Examiner as teaching "targeting TNF (page 413) and the use of methotrexate (page 421) in the treatment of inflammatory bowel diseases".

At page 413, Markowitz *et al.* state that "TNF appears to be a proximal mediator of inflammation and shock." This, however, does not teach, with an expectation of success, "targeting TNF" in the treatment of inflammatory bowel diseases. In addition, although Markowitz *et al.* disclose the use of methotrexate in the treatment of inflammatory bowel disease, they do not teach or suggest co-administering a TNF antagonist and methotrexate to treat the disease. Thus, Markowitz *et al.* do not teach or suggest, with an expectation of success, treating inflammatory bowel disease (or other autoimmune or inflammatory disease, including rheumatoid arthritis) in an individual by co-

administering methotrexate and a TNFα antagonist to the individual.

Brahn *et al.*

Brahn *et al.* disclose in their abstract the results from a study on the effects of TNFα, methotrexate, or combination cyclosporin and methotrexate therapy on collagen arthritis. They report that (1) TNFα therapy is "not therapeutically beneficial and may actually exacerbate collagen arthritis"; (2) methotrexate therapy is ineffectual at treating collagen arthritis; and (3) combination cyclosporin and methotrexate therapy attenuates the disease. Thus, Brahn *et al.* clearly teach away from the claimed invention.

Cohen *et al.*

Cohen *et al.* disclose the use of cyclosporine A or methotrexate in the treatment of patients with refractory rheumatoid arthritis.

Pascalis *et al.*

Pascalis *et al.* disclose the use of combined cyclosporine A, fluocortolone and methotrexate in the treatment of patients with rheumatoid arthritis.

The Combination of References

In support of the rejection, the Examiner states:

> [T]he prior art taught the claimed TNF-specific antagonists and methotrexate as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said inflammatory antagonists to achieve the same desired goals in treating arthritis and Crohn's disease . . . The combination of references provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition.

> One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo.

Applicants respectfully disagree with the Examiner's conclusion that the claimed invention was obvious.

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the Applicants' disclosure. Id.

Applicants demonstrated the unexpected result that combination therapy with methotrexate and a TNFα antagonist produced unexpected synergistic effects between methotrexate and the TNFα antagonist (see, e.g., Figures 1A, 2A, 3A, 4A, 5A and Table 4 of the specification). Applicants also demonstrated the unexpected result that significantly reduced immunogenicity of anti-TNFα antibodies was obtained with combination therapy with methotrexate (see, e.g., page 57, line 30 to page 60, line 4, including Table 6, of the specification). The magnitude of these results, particularly in the treatment of RA, could not have been predicted from the cited references.

It is by now well settled that significant improvements in combination therapies can rebut a *prima facie* case of obviousness. See In re Kollman, 201 U.S.P.Q. 193 (C.C.P.A. 1979). See also M.P.E.P. § 716.02(a). That is, greater than expected results is evidence of nonobviousness. See, e.g.,

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M.P.E.P. § 716.02(a). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating synergism). Merck & Co. Inc. v. Biocraft Laboratories Inc., 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989); In re Luvisi and Nohejl, 144 U.S.P.Q. 646 (C.C.P.A. 1965).

As discussed above, although Le *et al.* state that TNF antagonists can be administered either as individual therapeutic agents or in combination with other therapeutic agents (Le *et al.*, col. 35, l. 25-28), this would not have led one of ordinary skill in the art to expect that such administration would produce the results described in the subject application, particularly synergistic effects. The Le *et al.* patent does not specify the co-administration of a TNF antagonist and methotrexate.

In addition, as discussed above, although the Aggarwal *et al.* patent indicates that when employed together, TNF antagonists and other anti-inflammatory agents (e.g., cyclosporin) can be administered in lesser dosages than when used alone (Aggarwal *et al.*, col. 7, l. 65-67), this would not have led one of ordinary skill in the art to expect that such administration would produce synergistic effects. In fact, Aggarwal *et al.* do not specifically specify the co-administration of a TNF antagonist and methotrexate.

Similarly, none of the secondary references cited by the Examiner (Barrera *et al.*, Kozarek *et al.*, Markowitz *et al.*, Brahn *et al.*, Cohen *et al.*, and Pascalis *et al.*) would lead one of ordinary skill in the art to expect that the results described in this application, particularly synergistic effects, would be obtained by combination therapy with methotrexate and a TNFα antagonist. In fact, Brahn *et al.*, who disclose that combination cyclosporin and methotrexate therapy attenuates arthritis, clearly teach away from the claimed invention.

Thus, the cited references in combination also would not lead one of ordinary skill in the art to expect that synergistic

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effects would be obtained by combination therapy with methotrexate and a TNFα antagonist.

In summary, one of ordinary skill in the art would not have been able to predict, given the cited references, the unexpected results obtained by Applicants by combination therapy with methotrexate and a TNFα antagonist. That is, one of ordinary skill in the art would not have been able to predict, given the cited references, whether combination therapy with methotrexate and a TNFα antagonist would provide a greater degree of protection (synergy), particularly against rheumatoid arthritis, than treatment with each reagent alone. Thus, withdrawal and reconsideration of this rejection under 35 U.S.C. § 103 are respectfully requested.

Provisional Rejection of Claims 1-3 and 5-31 Under the Doctrine of Obviousness-Type Double Patenting

Claims 1-3 and 5-31 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting because it is the Examiner's assessment that the claims are "unpatentable over Claims 15-31 of copending application U.S. Serial No. 08/607,419 in view of the art recognized use of immunosuppressive therapy encompassing cyclosporin and methotrexate in arthritis and Crohn's disease and xanthine derivatives in the treatment or reduction of TNF-mediated diseases".

Applicants intend to file a terminal disclaimer without prejudice upon resolution of the remaining issues. It is noted that this is a provisional rejection as neither application has been allowed or patented.

Common Ownership

The Examiner states that commonly assigned U.S. Serial No. 08/607,419 would form the basis for a rejection of Claims 1-3 and 5-31 under 35 U.S.C. § 103:

> if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. . . . [T]he assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter.

The present invention and the invention of U.S. Serial No. 08/607,419 were commonly owned at the time the present invention was made. Thus, U.S. Serial No. 08/607,419 does not qualify as prior art under 35 U.S.C. § 102(f) or (g). As such, U.S. Serial No. 08/607,419 does not form the basis for a rejection of Claims 1-3 and 5-31 under 35 U.S.C. § 103.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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Dated: June 8, 1998

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